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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0050693

DATE: April 25, 2002

MEMORANDUM

SUBJECT: **TEBUFENPYRAD** - 1st Report of the Hazard Identification Assessment Review Committee.

FROM: Pamela M. Hurley
Registration Action Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Pamela M. Hurley, Risk Assessor
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 090102

On March 21, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for **Tebufenpyrad** with regard to the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The acute and chronic Reference Doses (RfDs) were not selected because there are no food uses. The Registration Petition is only for an Experimental Use Permit (EUP) for tebufenpyrad as an acaricide/insecticideon non-edible greenhouse ornamental crops. This was the first evaluation by the HIARC. The potential for increased susceptibility of infants and children from exposure to **Tebufenpyrad** was not evaluated as required by the Food Quality Protection Act (FQPA) of 1996 because there are no food uses. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Elizabeth Doyle, Pamela Hurley, Elizabeth Mendez, David Nixon, Ayaad Assaad, John Liccione, Jonathan Chen, Virginia Fornillo, and Jess Rowland

Member(s) in absentia: Paula Deschamp

Data evaluation prepared by: Virginia Dobozy (RRB1)

Also in attendance were: Karen Whitby (RAB1), Steven Weiss (RRB3), P.V. Shah (RAB1), Tom Bloem (RAB1), Dana Vogel (RAB1), Carole Christensen (RRB2)

Report Presentation

Pamela M Hurley

Pamela M. Hurley
Toxicologist

1. INTRODUCTION

On March 21, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for **Tebufenpyrad** with regard to the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The acute and chronic Reference Doses (RfDs) were not selected because there are no food uses. The Registration Petition is only for an Experimental Use Permit (EUP) for tebufenpyrad as an acaricide/insecticide on non-edible greenhouse ornamental crops. This was the first evaluation by the HIARC. The potential for increased susceptibility of infants and children from exposure to **Tebufenpyrad** was not evaluated as required by the Food Quality Protection Act (FQPA) of 1996 because there are no food uses. The conclusions drawn at this meeting are presented in this report.

2. FQPA HAZARD CONSIDERATIONS

FQPA hazard considerations were not addressed because there are no food uses.

3. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD)

The acute reference dose is not applicable because there are no food uses.

2. Chronic Reference Dose (cRfD)

The chronic reference dose is not applicable because there are no food uses.

3. Incidental Oral Exposure: Short-Term (Any Duration)

The incidental oral endpoints are not applicable because there are no residential uses.

4. Dermal Absorption

Dermal Absorption Factor: 4%. There are no dermal absorption studies available. An estimation of a dermal absorption factor can be made by comparing the LOAEL of 1000 mg/kg/day from the 21-day dermal toxicity study in the rabbit with the LOAEL of 40 mg/kg/day from the prenatal developmental toxicity study in the rabbit. In both these studies, decreases in body weight gain and food consumption were observed at these LOAELs.

5. Dermal Exposure: Short- and Intermediate - Term (1- 30 days and 1 - 6 Months)

Study Selected: 21-day dermal study in the rabbit Guideline #: OPPTS 870.3200

MRID No.: 43309314

Executive Summary: In a 21-day dermal toxicity study (MRID 43309314), groups of 6 male and 6 female New Zealand White rabbits were treated with MK-239 (>99% a.i., Lot/Batch No. 8J-10) in carboxymethyl cellulose in distilled water by dermal occlusion at doses of 0, 40, 200, or 1000 mg/kg/day, 6 hours/day, 5 days/week for 3 weeks. No mortality was observed. No clinical signs of toxicity were observed in animals treated with 40 or 200 mg/kg/day. One high-dose male appeared thin during weeks 2 and 3, and several high-dose animals of both sexes passed few feces during weeks 1-3. Body weight gains of high-dose males and females were decreased by 55% and 19%, respectively, while food consumption for these groups was decreased by 22% and 12%, respectively. There were no toxicologically significant treatment-related abnormalities in ophthalmoscopy, organ weights, clinical biochemistry, hematology, or urinalysis. There were no treatment-related pathological abnormalities.

Under conditions of this study, the systemic NOAEL for MK-239 was 200 mg/kg/day; the LOAEL was 1000 mg/kg/day based on decreased body weight gain and food consumption in male and female New Zealand White rabbits. There was no evidence of dermal toxicity at 1000 mg/kg/day, the highest dose tested.

This 21-day dermal toxicity study in the rabbit is **acceptable/guideline** and **satisfies** the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in the rabbit.

Dose and Endpoint for Risk Assessment: NOAEL of 200 mg/kg/day based on decreased body weight gain and food consumption at the LOAEL of 1000 mg/kg/day.

Comments about Study/Endpoint: The study duration and route of administration are appropriate for this risk assessment. A comparison of the subchronic feeding study in the rat and the chronic feeding study in the rat indicates that the effects observed in the chronic study at the NOAEL of the subchronic study are not significant enough at the 3- and 6-month timepoints to warrant an additional uncertainty factor for extrapolation from a 21-day dermal study to a longer term dermal study. Thus, the 21-day dermal study provides an appropriate endpoint for intermediate-term exposure. In addition, this endpoint is protective of any developmental effects observed in either the rat or the rabbit developmental toxicity studies. In these studies, developmental effects were only observed in the presence of maternal toxicity. In addition, using a dermal absorption estimate of 4%, the developmental NOAEL of 15 mg/kg/day from the rabbit study

effectively becomes a NOAEL of 375 mg/kg/day and the developmental NOAEL of 50 mg/kg/day from the rat study effectively becomes a NOAEL of 1250 mg/kg/day.

6. Dermal Exposure Long-Term (> 6 Months)

Study Selected: Combined chronic toxicity/carcinogenicity in rats
Guideline #: OPPTS 870.4300

MRID No.: 43309320

Executive Summary: In a combined chronic toxicity/oncogenicity study (MRID 43309320), MK-239 (99.5% a.i.) was administered in the diet to 55 male and 55 female F344 rats at concentrations of 0, 5, 20, 150, or 300 ppm (0, 0.21, 0.82, 6.52, 13.43 mg/kg/day for males and 0, 0.26, 1.01, 8.13, 16.95 mg/kg/day for females) for 104 weeks. An additional ten animals of each sex in each dose group were included for interim sacrifice at 52 weeks.

No treatment-related effects occurred in male or female rats fed the 5- or 20-ppm test diets. At 150 ppm, male and female rats showed treatment-related effects including decreases in mean body weights (≤10 and ≤8%, respectively) and body weight gain (8 and 12%, respectively), increases in absolute (131 and 137%, respectively) and relative liver weights (up to 142 and 150%, respectively), and an increase in the incidence of hepatocellular hypertrophy (11 and 44% in males and females, respectively). In addition, serum alkaline phosphatase activity was increased in both sexes fed the 150-ppm test diet. Females fed the 150-ppm diet showed signs of a slight microcytic anemia, and they had an increased incidence of ovarian cysts. Similar, but more severe effects were seen at the 300-ppm dietary level in both sexes. At 300 ppm, lesions also occurred in the pancreas (focal acinar cell hyperplasia) in male (15/55 vs 1/54 in controls) and female rats (11/54 vs 1/55 in controls) and in the mammary gland (acinar hyperplasia) of female rats (11/55 vs 1/55 in controls).

The LOAEL for MK-239 is 150 ppm (6.52 and 8.13 mg/kg/day for males and females, respectively), based on decreased body weights and body weight gain and liver toxicity in both sexes and a slight microcytic anemia and effects on the ovary in females. The corresponding NOAEL is 20 ppm (0.82 and 1.01 mg/kg/day, respectively).

The potential carcinogenicity of MK-239 was exhibited by an increased incidence of hepatocellular adenomas in male rats at 150 (7%, N.S.) and 300 ppm (18%, $p<0.01$) compared with the incidence in concurrent controls (0%). The incidence of hepatocellular adenomas in the historical control animals was 0 - 8%. The incidence of pituitary adenomas/carcinomas was significantly increased in females at 300 ppm. The historical incidence for the combined incidence was not given, but the incidence for

adenoma (43%) and carcinomas (4%) separately were within the range of historical controls (adenomas, 22.9-61.7%; carcinomas, 0-16%). Therefore, pituitary adenomas/carcinomas are not considered to be treatment related. The incidence of thyroid parafollicular carcinomas and adenomas/carcinomas combined were significantly elevated at the 20-ppm dose level in females, but the lack of a significant increase at 150 and 300 ppm suggest that this lesion is not treatment related. The dosing was considered to be adequate for both male and female rats.

This chronic toxicity/carcinogenicity study in the rats is **Acceptable (Guideline)** and satisfies the guideline requirement for a chronic/carcinogenicity study (83-5; OPPTS 870.4300) in rats.

Dose and Endpoint for Risk Assessment: NOAEL of 0.82/1.01 mg.kg/day for males and females, respectively based on decreased body weight and body weight gain and liver toxicity in both sexes and a slight microcytic anemia and effects on the ovary in females and the LOAEL of 6.52/8.13 mg/kg/day

Comments about Study/Endpoint: There are no dermal studies of the appropriate duration for this risk assessment. Therefore, an oral study was selected. The duration of the study is appropriate for this endpoint. Since the study selected was conducted with oral administration, a dermal absorption factor of 4% should be applied.

7. Inhalation Exposure: Short -Term (1- 30 days)

Study Selected: Prenatal developmental toxicity study in rats Guideline: OPPTS 870.3700a

MRID No.: 43309317

Executive Summary: In a developmental toxicity study (MRID 43309317), tebufenpyrad (technical, 99% a.i.) in 0.5% w/v aqueous tragacanth mucilage was administered by gavage to 26 female CD (Sprague-Dawley) rats at dose levels of 0, 15, or 50 mg/kg/day and to 30 female CD (Sprague Dawley) rats at 90 mg/kg/day from days 6 through 15 of gestation.

Slight maternal toxicity was demonstrated at 90 mg/kg/day as clinical signs of toxicity which were characterized as reduced activity in 13.3% of the dams between days 8-11 and an increased incidence of dams with brown staining on the head and/or body surface (40% vs. 3.8% in controls, $p<0.01$). Brown staining was also observed in 15.4% of the 50 and 15 mg/kg/day animals (not statistically significant). No other clinical signs of toxicity were recorded at any treatment level. At 90 mg/kg/day, maternal body weight gains decreased significantly ($p<0.05$-$p<0.001$) during the first three days of treatment (↓21%) with recovery during the remaining treatment and post-treatment periods compared to controls. Body weight gain of 50 mg/kg/day dams was significantly reduced

($p<0.05$) during the first day of treatment only (↓43%) and was comparable to the controls thereafter. Food consumption was decreased (14%) days 6-8 in females at 90 mg/kg/day.Water consumption was slightly but significantly increased ($p<0.01$) in high-dose females during the first three days, compared to controls. The mid- and high-dose groups exhibited significantly increased ($p<0.01$, 0.001) water consumption during the post-treatment period. There were no treatment-related effects on mortality, gross pathology, or cesarean parameters at any dose level. **The maternal LOAEL is 50 mg/kg/day based on decreased body weight gain and increased water consumption. The maternal NOAEL is 15 mg/kg/day.**

Developmental toxicity was noted at 90 mg/kg/day and characterized as a dose-dependent increase in the fetal and litter incidence of additional ribs (18.7% fetuses, 66.7% litters at high dose with 14/14 ribs vs. 8.7% fetuses, 30.8% litters for controls). The increase at the high dose was shown to be statistically significant ($p<0.05$), however, it is not clear from the information presented if the statistics were performed on the litter or fetal incidence values. **The developmental LOAEL is 90 mg/kg/day, based on an increase in the fetal and litter incidence of additional ribs. The developmental NOAEL is 50 mg/kg/day.**

This developmental toxicity study in the rat is classified **acceptable/guideline** and satisfies the guideline requirements for a developmental toxicity study in rats.

Dose/Endpoint for Risk Assessment: Maternal NOAEL of 15 mg/kg/day based on decreased body weight gain and increased water consumption at a LOAEL of 50 mg/kg/day.

Comments about Study/Endpoint: This study is an appropriate duration for this exposure. The endpoint is supported by both the rat and rabbit developmental toxicity studies as both have the same maternal NOAEL. In addition, any potential developmental effects are protected as the maternal NOAELs are identical to the lowest developmental NOAEL. The study selected was conducted via oral administration. Inhalation absorption is assumed to be equivalent to oral absorption.

8. Inhalation Exposure: Intermediate-Term (1- 6 Months)

Study Selected: 90-Day Capsule Study in the Dog Guideline OPPTS 870.3150

MRID No.: 43309313

Executive Summary: In a subchronic oral toxicity study [MRID 43309313], groups of five male and five female beagle dogs were given technical MK-239 [98.9% a.i., Lot J-10] in gelatin capsules at doses levels of 0 [empty gelatin capsules], 2, 10, or 20

mg/kg/day for 93 days [males]/91 days [females].

No animals died during the study. The most significant toxic effect of MK-239 was an increased incidence and duration of food vomiting and/or diarrhea in both sexes at 10 and 20 mg/kg/day, particularly during the first two months of treatment. This was accompanied by slight, statistically non-significant increases in the incidence of colon focal mucosal congestion in 10 and 20 mg/kg/day males (2/5 and 3/5, respectively, vs. 0/5 for controls), in stomach focal mucosal congestion in 20 mg/kg/day males (2/5 vs.1/5 for controls), and in stomach focal mucosal edema in 20 mg/kg/day females (1/5 vs. 0/5 for controls). Although these histological findings were minor, they were consistent with a previous range-finding study where gastric erosion was seen in both sexes at doses ≥ 20 mg/kg/day and indicate that MK-239 acts as a gastrointestinal irritant in dogs. The absolute and/or relative ovary weights of 20 mg/kg/day females were significantly lower than controls, although this effect was not considered toxicologically significant since it was not dose-related and had no histological correlates. The transiently lower weight gains in dogs given 20 mg/kg/day (week 1 and/or 4 in both sexes; $p<0.05$ or 0.01) were likely due to the diarrhea and/or vomiting; the overall 13-week body-weight gain was comparable to controls.

The NOAEL for both male and female dogs was 2 mg/kg/day. The LOAEL was 10 mg/kg/day based on an increased incidence of diarrhea and/or vomiting in males and females. The actual dosages the high- and mid-dose animals received are uncertain because some of the compound was likely regurgitated.

This study is classified as **acceptable/guideline** and **satisfies** the guideline requirements (870.3150; 82-1b) for a subchronic oral toxicity study in a non-rodent species (dog).

Dose/Endpoint for Risk Assessment: NOAEL of 2 mg/kg/day based on an increased incidence of diarrhea and/or vomiting in males and females at the LOAEL of 10 mg/kg/day. The actual dosages received at 10 mg/kg/day are uncertain because some of the compound was likely regurgitated.

Comments about Study/Endpoint: There are no inhalation studies of the appropriate duration for this risk assessment. Therefore, an oral study was selected. The study duration is appropriate for this endpoint and the dog is the most sensitive species. The effects in the dog study appear to be related to irritation. Irritation in the gut is considered to be a possible predictor of irritation in the lungs. Therefore, the oral dog study is considered to be appropriate for an inhalation endpoint. Inhalation absorption is assumed to be equivalent to oral absorption.

9. Inhalation Exposure: Long-Term (> 6 Months)

Study Selected: 1-Year Capsule Study in the Dog §870.4100

MRID No.: 43309315

Executive Summary: In a chronic toxicity study (MRID 43309315), MK-239 Technical (98.9% a.i.) was administered to groups of 5 male and 5 female beagle dogs orally via gelatin capsules. The doses were 0, 1, 6, or 20 mg/kg of body weight/day and were administered 7 days/week for 12 months (52 weeks).

No unscheduled mortalities occurred during the study. Incidences of vomiting food and diarrhea/loose stool were increased in the males and females from the 6 and 20 mg/kg/day groups. There were no statistically significant changes in mean body weight or mean body weight gain, although decreased body weight gain was observed in males and females (57% and 50% of control, respectively) during the first week of treatment. Overall body weight gain was decreased in males at 20 mg/kg/day (83% control) and in all treated females (69%, 75%, 75% of control in 1, 6 and 20 mg/kg/day groups, respectively). The lack of statistical significance and dose response in females makes this finding questionable toxicologically. The ophthalmoscopic examinations, hematology, clinical chemistry and urinalysis demonstrated no changes of toxicological importance. The absolute and relative prostate weights were decreased by 40.5 and 35.9%, respectively, and absolute and relative weights testis were increased by 15.4 and 25%, respectively, in the 20 mg/kg/day group. The absolute and relative adrenal weights in the males from the 20 mg/kg/day group were nonstatistically significantly increased, 7.4 and 20.0%, respectively. Gross pathology exhibited thickened gastric mucosa in the pyloric region in 1 and 2 females from the 6 and 20 mg/kg/day groups, respectively. Histopathological evaluation revealed erosion in the pyloric region in 1/5 females from the 6 and 20 mg/kg/day groups, chronic gastritis in the pyloric region in 1/5 males and 1/5 females at 6 mg/kg/day and in 2/5 males and 2/5 females at 20 mg/kg/day groups. Focal cystic acinar dilatation in the prostate was slightly increased at 20 mg/kg/day (1/5, 1/5, 1/5 and 3/5 in males at 0, 1, 6 and 20 mg/kg/day males, respectively). **Based on the incidences of vomiting and diarrhea/loose stools and thickened gastric mucosa and chronic gastritis in the pyloric region, the LOAEL is 6 mg/kg/day and the NOAEL is 1 mg/kg/day.**

This chronic toxicity study is classified as **Acceptable (guideline)** and does satisfy the guideline requirement for a chronic oral study (83-1b) in dogs.

Dose/Endpoint for Risk Assessment: NOAEL of 1 mg/kg/day based on the incidences of vomiting and diarrhea/loose stools and thickened gastric mucosa and chronic gastritis in the pyloric region at the LOAEL of 6 mg/kg/day.

Comments about Study/Endpoint: There are no inhalation studies of the appropriate duration for this risk assessment. Therefore, an oral study was selected. The study duration is appropriate for this endpoint and the dog is the most sensitive species. The effects in the dog study appear to be related to irritation. Irritation in the gut is considered to be a possible predictor of irritation in the lungs. Therefore, the chronic oral dog study is considered to be appropriate for the long-term inhalation endpoint. Inhalation absorption is assumed to be equivalent to oral absorption.

10. Margins of Exposure

The target Margins of Exposure (MOEs) for **occupational** exposure risk assessments are as follows:

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Dermal	100	100	100
Inhalation	100	100	100

The MOEs for dermal and inhalation exposures may be combined for short-term occupational exposure risk assessment because the toxicity endpoints for these routes of exposure are the same. The MOEs for dermal and inhalation exposures may not be combined for intermediate- and long-term exposure risk assessments because the toxicity endpoints for these routes of exposure are not the same.

The target MOEs for **residential** exposure risk assessments will be determined by the FQPA Safety Factor Committee.

11. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. There are no residential or food exposures for this chemical. Therefore, aggregate risks will not be estimated.

4. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 43309320

Executive Summary: In a combined chronic toxicity/oncogenicity study (MRID 43309320), MK-239 (99.5% a.i.) was administered in the diet to 55 male and 55 female F344 rats at concentrations of 0, 5, 20, 150, or 300 ppm (0, 0.21, 0.82, 6.52, 13.43 mg/kg/day for males and 0, 0.26, 1.01, 8.13, 16.95 mg/kg/day for females) for 104 weeks. An additional ten animals of each sex in each dose group were included for interim sacrifice at 52 weeks.

No treatment-related effects occurred in male or female rats fed the 5 or 20 ppm test diets. At 150 ppm, male and female rats showed treatment-related effects including decreases in mean body weights (≤10 and ≤8%, respectively) and body weight gain (8 and 12%, respectively), increases in absolute (131 and 137%, respectively) and relative liver weights (up to 142 and 150%, respectively), and an increase in the incidence of hepatocellular hypertrophy (11 and 44% in males and females, respectively). In addition, serum alkaline phosphatase activity was increased in both sexes fed the 150 ppm test diet. Females fed the 150 ppm diet showed signs of a slight microcytic anemia, and they had an increased incidence of ovarian cysts. Similar, but more severe effects were seen at the 300 ppm dietary level in both sexes. At 300 ppm, lesions also occurred in the pancreas (focal acinar cell hyperplasia) in male (15/55 vs 1/54 in controls) and female rats (11/54 vs 1/55 in controls) and in the mammary gland (acinar hyperplasia) of female rats (11/55 vs 1/55 in controls).

The LOAEL for MK-239 is 150 ppm (6.52 and 8.13 mg/kg/day for males and females, respectively), based on decreased body weights and body weight gain and liver toxicity in both sexes (increased liver weight, hepatocyte hypertrophy and increased alkaline phosphatase activity) and a slight microcytic anemia and effects on the ovary in females. The corresponding NOAEL is 20 ppm (0.82 and 1.01 mg/kg/day, respectively).

The potential carcinogenicity of MK-239 was exhibited by an increased incidence of hepatocellular adenomas in male rats at 150 (7%, N.S.) and 300 ppm (18%, $p<0.01$) compared with the incidence in concurrent controls (0%). The incidence of hepatocellular adenomas in the historical control animals was 0 - 8%. The incidence of pituitary adenomas/carcinomas was significantly increased in females at 300 ppm. The historical incidence for the combined incidence was not given, but the incidence for adenoma (43%) and carcinomas (4%) separately were within the range of historical controls (adenomas, 22.9-61.7%; carcinomas, 0-16%). Therefore, pituitary adenomas/carcinomas are not considered to be treatment related. The incidence of

thyroid parafollicular carcinomas and adenomas/carcinomas combined were significantly elevated at the 20 ppm dose level in females, but the lack of a significant increase at 150 and 300 ppm suggest that this lesion is not treatment related. The dosing was considered to be adequate for both male and female rats.

This chronic toxicity/carcinogenicity study in the rats is **Acceptable (Guideline)** and satisfies the guideline requirement for a chronic/carcinogenicity study (83-5; OPPTS 870.4300) in rats.

Discussion of Tumor Data. The only neoplastic lesion showing a statistically significant increase in incidence in male rats was hepatocellular adenomas at the 300 ppm dose level [10/55 (18%) vs 0% for controls, $p<0.01$]; the incidence at 150 ppm was increased [4/54 (7.4%)] but did not achieve statistical significance compared with controls. The incidence of hepatocellular adenomas in historical control animals was 0-8%. In female rats, the incidence of hepatocellular adenomas was significantly increased at the 150 ppm dose level [5/55 (9%) vs 0% for controls, $p<0.05$]; the increase at 300 ppm [3/55(5%)] was less than that at 150 ppm and did not achieve statistical significance compared with the control incidence. The incidences of pituitary adenomas [23/54 (43%)] and adenomas/ carcinomas combined [25/54 (46%)] showed nonsignificant increases at the 300 ppm dose level in female rats compared with the incidences in controls [15/53 (28%) and 16/53 (30%), respectively]. The incidence of adenomas was within the historical control mean and range (43%, 22.9-61.7%). There were no historical control data for the incidence of combined pituitary adenomas/carcinomas but the incidence for adenomas (43%) and carcinomas (4%) in the MK-239 treated animals was within the range of historical controls (adenomas, 22.9-61.7%; carcinomas, 0-16%). The incidence of thyroid parafollicular carcinomas and adenomas/carcinomas combined were significantly elevated at the 20 ppm dose level in females, but the lack of a significant increase at 150 and 300 ppm suggest that this lesion is not treatment related.

Adequacy of the Dose Levels Tested: The doses are considered adequate for testing the carcinogenic potential of MK-239. At the high dose of 300 ppm, body weights were non-statistically significantly decreased in males (10-15%) and females (5-12%). Body weight gains were non-statistically significantly decreased 19% and 12% in males and females, respectively, during weeks 0-13. From weeks 0-52, the decreases were statistically significantly decreased in males (20%) and females (22%). Body weights gains were also significantly decreased in males and females (6%) in the 150 ppm group during this time period. For the overall (weeks 0-104) study, body weight gain in males in the 150 and 300 ppm groups were significantly decreased 8% and 21%, respectively; female body weight gain in these groups was significantly decreased 12% and 33%, respectively. Increases in absolute and relative liver weights, along with hepatocellular hypertrophy were observed in both males and females at 150 and 300 ppm.

2. Carcinogenicity Study in Mice

MRID No. 43309316

Executive Summary: In a 78-week oncogenicity feeding study, MK-239 was administered in the diet to 64 male and 64 female CD-1 mice per group at 0, 30, 500, or 1000 ppm. Twelve male and 12 female mice from each group were sacrificed after 52 weeks of treatment to provide interim data. The concentrations corresponded to average doses of about 0, 3.6, 64.4, and 132.1 mg/kg/day for males; and 0, 4.2, 71.3, and 162.0 mg/kg/day for females. No statistically significant, treatment-related differences in survival or in clinical findings were seen in treated animals compared to the control groups. The group mean body weights were significantly ($p<0.05$) decreased at 1000 ppm after 28, 52 and 78 weeks of treatment in both sexes and also after 14 weeks of treatment in females. Male group mean body weights at 1000 ppm were 90% of the control group mean body weight at 52 weeks and 91% at 78 weeks; female group mean body weights were 87% of the control group mean body weights at 52 weeks and 85% at week 78. The group mean body weight gain was significantly ($p<0.01$) decreased in both sexes to 61-75% of the control weight gain at 1000 ppm after both 52 and 78 weeks of treatment. The body weight gain was slightly decreased in females at 500 ppm (91% of control at 52 weeks, 87% at 78 weeks); and was significantly ($p<0.001$) decreased in males at 52 weeks (84% of control). The weight gain in males at 78 weeks was 94% of the control weight gain. The food intake was not decreased in the treated animals at any dose.

The platelet counts were significantly increased in females at 1000 ppm after 52 and 78 weeks of treatment (121 and 112% of control, respectively). The counts were slightly higher than the historic controls presented in the study, but were within the normal range reported for this strain of mouse by the Charles River Laboratories. Although a few other hematology parameters were significantly different when statistically compared to the control values for this study, they were within the normal range for mice of this strain when compared to the historical controls, and therefore, the observed changes are of doubtful toxicological significance.

Significant ($p<0.01$) increases in the group mean absolute (109 and 117% of controls, respectively) and relative (114 and 123% of controls, respectively) kidney and liver weights were seen in females at 500 ppm and at 1000 ppm (112 and 120% of controls for absolute weights, respectively; 129 and 139% of controls for relative weights, respectively). No treatment-related increase in the incidence of any lesion in the liver or kidney was found that corresponded to the organ weight changes. The group mean relative (organ to body) weights of brain and heart of both sexes were increased at 500 and 1000 ppm, but no corresponding histopathological changes were seen. The changes in relative weights most likely reflect the decrease in body weight gain at 500 and 1000 ppm. An increase in the incidence of thickened stomach wall from 1.9% in the controls

to 15.4% in males at 1000 ppm was seen, however, there was no clear dose-response relationship. Increases in the incidences of glandular stomach dysplasia were seen on microscopic examination that were statistically significant in females at all dose levels compared to the control group (1.9% in controls, 17.3, 15.4, and 15.4%, respectively at the low, mid, and high doses). However, female control animals in historical studies had an incidence of stomach dysplasia of 13.4%, which indicates that the statistical significance of this lesion in the current study is due to an unusually low incidence for stomach dysplasia in the female control group. The increase was not statistically significant in males (13.7% in controls, 15.4% at 30 ppm, 19.6% at 500 ppm, and 23.5% at 1000 ppm), but it appeared to be dose-dependent and was associated with the thickening of the stomach wall seen in males at 1000 ppm on gross examination.

The Lowest-Observed-Adverse -Effect-Level (LOAEL) of 500 ppm (64.4 mg/kg/day for males; 71.3 mg/kg/day for females) was based on decreased body weight gain with no decrease in food consumption. A No-Observed-Adverse-Effect-Level (NOAEL) of 30 ppm (3.6 mg/kg/day for males; 4.2 mg/kg/day for females) was identified.

No increases in tumor incidences were seen in treated animals at any dose. The doses were adequate for testing the carcinogenic potential of MK-239.

The study is classified as Acceptable (Guideline) and satisfies the guideline requirements for a carcinogenicity feeding study in mice (83-2; OPPTS 870.4200).

Discussion of Tumor Data In a 78-week oncogenicity feeding study, MK-239 (99.5%) was administered in the diet to 64 male and 64 female CD-1 mice per group at 0, 30, 500, or 1000 ppm (0, 3.6, 64.4, and 132.1 mg/kg/day for males; and 0, 4.2, 71.3, and 162.0 mg/kg/day for females). There was no treatment-related increase in tumor incidence in the study.

Adequacy of the Dose Levels Tested: The doses were considered adequate for testing the carcinogenic potential of MK-239. Male group mean body weights at 1000 ppm were 90% of the control group mean body weight at 52 weeks and 91% at 78 weeks; female group mean body weights were 87% of the control group mean body weights at 52 weeks and 85% at week 78. The group mean body weight gain was significantly ($p<0.01$) decreased in both sexes to 61-75% of the control weight gain at 1000 ppm after both 52 and 78 weeks of treatment. The body weight gain was slightly decreased in females at 500 ppm (91% of control at 52 weeks, 87% at 78 weeks); and was significantly ($p<0.001$) decreased in males at 52 weeks (84% of control). The weight gain in males at 78 weeks was 94% of the control weight gain. The food intake was not decreased in the treated animals at any dose.

Classification of Carcinogenic Potential: The HIARC noted that there is an increase in hepatocellular adenomas. This chemical has been referred to the CARC for further assessment for carcinogenic potential.

5. MUTAGENICITY

The HIARC did not provide any conclusions on the concern for mutagenicity resulting from exposure to tebufenpyrad. All of the mutagenicity studies were negative except for the in vitro cytogenetic studies. In those studies, it was concluded that tebufenpyrad exhibited reproducible but weak evidence of a clastogenic response but only after prolonged exposure to cytotoxic doses and only in the absence of S9 activation.

Gene Mutation - Microbial Systems - Salmonella/mammalian activation gene mutation assay; OPPTS 870.5100 [§84-2]

Executive Summary: In a *Salmonella*/microsome plate incorporation assay (MRID No. 43309321), *S.typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 and *Escherichia coli* strain WP2(uvrA) were exposed to MK-239 at concentrations of 50, 158, 500, 1580 and 5000 µg/plate, with and without exogenous metabolic activation. Preparations for metabolic activation were made from Aroclor 1254 induced male CD rat livers. The test material was delivered in DMSO.

Cytotoxicity, as evidenced by a slight thinning of the background lawn of bacteria, was seen at 5000 µg/plate with all strains. Positive and solvent controls were acceptable. **There was no evidence of induced revertant colonies over solvent control values in any strain at any dose tested, either with or without S9 mix.**

This study is classified as an acceptable/guideline study. It satisfies the guideline requirements for a gene mutation study [84-2(a); OPPTS 870.5100].

Gene Mutation - Mammalian Systems - *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Chinese hamster V79 cells; OPPTS 870.5300 [§84-2]; OECD 476.

Executive Summary: In a forward mutation study at the HGPRT locus in Chinese hamster V79 cells in culture (MRID No. 43309322, Batch No. 880222), cells were exposed to MK-239 (98.5%) under non-activated conditions at concentrations of 1.25, 2.5, 5, 10, 20, 30 µg/ml in the first assay and 2.5, 5, 10, 20, 30, 40 µg/ml in a second assay and under activated conditions to concentrations of 10, 20, 40, 60, 100, 150 µg/ml in the first assay and to 40, 60, 100, 150, 175, 200 µg/ml in a second assay. Preparations for metabolic activation were made from Aroclor 1254 induced male CD rat liver. The test material was delivered in DMSO.

MK-239 was tested to concentrations limited by cytotoxicity and solubility. Positive and solvent control values were appropriate. **No reproducible dose-related increase in mutation frequency was seen at the HGPRT locus in Chinese hamster V79 cells in this study, either with or without S9 mix.**

This study is classified as an **acceptable/guideline** study. It **satisfies** the guideline requirements for a gene mutation in mammalian cells study (84-2; OPPTS 870.5300).

Chromosome Aberrations: *In vitro* Mammalian Cytogenetics in cultured human lymphocytes OPPTS 870.5375 [§84-2]

Executive Summary: Two independently performed *in vitro* cytogenetic assays utilizing human lymphocytes as the target cell line were included in this submission (MRID 43309324). In an *in vitro* mammalian cell cytogenetic assay reported in 1994, human blood lymphocytes in culture were exposed to MK-239 (98.8% a.i.) at concentrations of 6, 8, 20, 40, 60, 80 µg/ml without exogenous metabolic activation (S9 mix) with an exposure time of 21 hours and to 8.25, 11, 27.5, 55, 82.5, 110 µg/ml with S9 mix with an exposure time of 4 hours. Cells were evaluated for chromosomal aberrations at 20, 40 and 80 µg/ml without S9 mix and at 27.5, 55 and 110 µg/ml with S9 mix. A confirmatory test was conducted using concentrations comparable to those evaluated in the initial test. An additional assay with a continuous exposure of 44 hours (without S9 activation) and a 20-hour continuous exposure with S9 activation was included.

In an *in vitro* mammalian cell cytogenetic assay reported in August 1990, human blood lymphocytes in culture were exposed to MK-239 (98.5% a.i.) at concentrations of 6.25, 12.5 and 25 µg/ml in the absence of S9 mix (2 hour exposure) and 12.5, 25 and 50 µg/ml in the presence of S9 mix (3 hour exposure). For both studies, preparations for metabolic activation were made from Aroclor 1254 induced rat liver and the test material was delivered in DMSO.

The test material was assayed to concentrations producing greater than a 50% depression of the mitotic index (MI). Positive and solvent control values were appropriate. In the 1994 study, no significant increase in chromosomal aberrations was seen at any concentration evaluated in the initial test, either with or without S9 mix. In the confirmatory 1994 assay, significant increases in chromosomal aberrations were seen at 20 and 40 µg/ml in the absence of a significant dose-response (primary sampling time without S9 mix) while a significant dose-response in the absence of a significant increase at any particular dose was noted at the delayed sampling time with S9 mix. Although some statistically significant increases in chromosomal aberrations were observed in MK-239 treated cells, failure to reproduce the results makes it unlikely that the increases are

biologically significant. **In the 1994 study, there was no clear evidence of a biologically significant induction of chromosomal aberrations by MK-239 at any concentration tested *in this study*, either with or without S9 mix.**

In the 1990 study, in the presence of S9 mix, no significant increases in the mean aberrant cell frequencies over solvent control values were seen at any dose of MK-239. In the absence of S9 mix, significant increases in mean aberrant cell frequencies over solvent control values were seen at all doses of MK-239 ($p < 0.001$). The increase in mean aberrant cell frequency at the highest dose tested, 25 µg/ml (3% versus 0.3% in the solvent control cultures), was lower than the increases seen at the two lower doses (7%), presumably due to cytotoxicity since there was an 84% reduction in the MI at this level. The effect was, however, significant ($0.05 > p > 0.01$). **In the 1990 study, MK-239 showed clastogenic activity at all concentrations tested in the absence of S9 mix but at no concentration tested in the presence of S9 mix.**

Overall, the combined data from both studies indicate that without S9 activation, the compound induced variable but nevertheless reproducible significant increases in the percentage of aberrant cells in two of three experiments using treatment times of 20-24 hours. In general, levels causing ≈ ≤ 40% decrease in the MI were negative, whereas concentrations causing ≥42% decrease in the MI induced significant effects with reproducibly flat dose response curves. Furthermore, the same type of aberrations (chromatid breaks) was induced in both studies. Based on these considerations, it is concluded that MK-239 exhibited reproducible but weak evidence of a clastogenic response but only after prolonged exposure to cytotoxic doses and only in the absence of S9 activation.

Both studies included in MRID # 43309324 are **acceptable/guideline** and **satisfy** the guideline requirements for an *in vitro* mammalian cell cytogenetic assay and meet the criteria for valid assays. The details presented in the remainder of this DER pertain to the 1994 study. A summary of the 1990 study is given in the Appendix.

Other Genotoxicity: Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell Cultures; OPPTS 870.5550 [§84-2]

Executive Summary: In an unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes (MRID No. 43309325), cultures of primary hepatocytes from a male Sprague-Dawley rat were exposed to MK-239 at concentrations of 0.0977, 0.309, 0.977, 3.09 and 9.77 µg/ml. The compound was delivered in DMSO and the cells exposed to the test material for approximately 17 hours. MK-239 was tested to a cytotoxic concentration and positive and solvent control values were appropriate. Two independent experiments were conducted. Four independent cultures, rather than six as stated in the

guidelines, were used for each test point and, prior to cell lysis, pairs of cultures were combined giving two replicate DNA extractions for each test point. The results were consistent within each experiment and showed no increase in tritiated thymidine incorporation over solvent control values at any concentration tested. The reduced number of replicate cultures is unlikely to have compromised the usefulness of the study. **As tested in this study, MK-239 did not induce DNA damage detectable by the UDS assay.**

This study is classified as an acceptable/guideline study. It satisfies the guideline requirements for an unscheduled DNA synthesis assay in mammalian cells in culture (84-2, OPPTS 870.5550).

6. HAZARD CHARACTERIZATION

Tebufenpyrad is a member of the pyrazole class of chemicals. The technical chemical is moderately acutely toxic by the oral route in the mouse (Toxicity Category II) and rat (Toxicity Category III). It is slightly toxic by the dermal route (Toxicity Category III) in the rat and relatively nontoxic by the inhalation route (Toxicity Category IV) in the rat. It is a minimal eye irritant but not a skin irritant in the rabbit. It was a mild dermal sensitizer in the guinea pig using the Maximization Test but negative in another study using the Buehler method.

Acute studies conducted with the 35.2% a.i. formulation demonstrated that the product was moderately toxic (Toxicity Category II) in the rat by the oral route, slightly toxic (Toxicity Category III) by the dermal and inhalation routes in the rat, a moderate eye irritant in the rabbit, a severe dermal irritant in the rabbit and negative for dermal sensitization in the guinea pig.

Tebufenpyrad was a gastric irritant in the dog studies with capsule administration. Vomiting and diarrhea/loose stools were observed at relatively low doses in the 90-day study (10 mg/kg/day) and the 1-year study (6 mg/kg/day). Thickened gastric mucosa and chronic gastritis were also reported in the 1-year study.

In the rat, decreased body weight gain and changes in the relative weights of multiple organs were observed in the 90-day study at higher doses (≈ 30 mg/kg/day). In the chronic toxicity/carcinogenicity study, body weight/body weight gain decreases were also observed, along with liver toxicity in both sexes and slight microcytic anemia and ovarian effects in females at lower doses (≈7 mg/kg/day). There was also a statistically significant increased incidence of hepatocellular adenomas in male rats at 13 mg/kg/day which exceeded the historical control incidence. There was no increased incidence of tumors in mouse carcinogenicity study at doses which were adequate for testing the carcinogenic potential of the chemical. The *in vitro* and *in vivo* mutagenicity studies were negative for evidence of gene mutation, chromosome

aberrations and other effects.

Decreased body weight gain and food consumption were observed at 1000 mg/kg/day in the 21-day dermal study; no dermal irritation was observed. No dermal absorption study was available.

There was no evidence of increased fetal susceptibility in the prenatal developmental studies in the rat and rabbit. In the prenatal developmental study in the rat, decreased body weight and increased water consumption were observed at 50 mg/kg/day. In the fetus, developmental toxicity (increase in fetal and litter incidence of additional ribs) was observed at 90 mg/kg/day. In the prenatal developmental study in rabbits, abortions, reduced body weight gain and food consumption were observed at 40 mg/kg/day. There were no developmental effects (other than the abortions) at this dose.

There was evidence of increased offspring susceptibility in the two-generation reproduction study in rats. There were no effects on maternal or reproduction parameters at approximately 19 mg/kg/day; however, there were effects (reduced body weights/body weight gain in male and female offspring and delayed vaginal opening in females) at this dose.

The metabolism study showed that >80% of tebufenpyrad was absorbed from the digestive system within 24 hours. The compound appeared to undergo rapid and extensive first-pass metabolism to primarily hydroxylated or carboxylated products with little of the parent compound appearing in the urine or feces. It was excreted primarily in the feces which accounted for ≥60% of the elimination; however, a significant portion was found in the urine (16-24%). More than 70% of the test material or its metabolites were eliminated within 72 hours of treatment and >90% was eliminated by 7 days. No accumulation of the parent compound or its metabolites was noted. A slight sex-specific difference in the metabolic disposition of the test material was found with male rats excreting more of the carboxylic acid metabolite on a relative basis while females tended to excrete more of the sulfate conjugate

7. DATA GAPS / REQUIREMENTS

90-Day Inhalation Study (870.3465) required since the use pattern indicates the potential for long-term inhalation exposure to workers. It will be used as an acaricide/insecticide on non-edible greenhouse ornamental crops.

8. ACUTE TOXICITY

Table 1: Acute Toxicity Data on Tebufenpyrad Technical

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1; OPPTS 870.1100	Acute Oral - Mouse	43309304	LD_{50} in males = 224 mg/kg; LD_{50} in females = 210 mg/kg Combined LD_{50} = 217 mg/kg	II
81-1 OPPTS 870.1100	Acute Oral - Rat	43309305	LD_{50} in males = 595 mg/kg; LD_{50} in females = 997 mg/kg Combined LD_{50} = 786 mg/kg	III
81-2; OPPTS 870.1200	Acute Dermal - Rat	43309306	LD_{50} > 2000 mg/kg in males and females	III
81-3; OPPTS 870.1300	Acute Inhalation - Rat	43309307	LD_{50} in males = 2.66 mg/L; LD_{50} in females = could not be calculated[a] Combined LD_{50} = 3.01 mg/L	IV
81-4; OPPTS 870.2400	Primary Eye Irritation - Rabbit	43309308	minimal irritant	III
81-5; OPPTS 870.2500	Primary Skin Irritation - Rabbit	43309309	not a dermal irritant	IV
81-6; OPPTS 870.2600	Dermal Sensitization - guinea pig	43309310	not a dermal sensitizer	
81-6; OPPTS 870.2600	Dermal Sensitization - guinea pig	43616611	mild dermal sensitizer	
81-8; OPPTS 870.6200	Acute Neurotoxicity - NA			

a In females treated at 0.38, 1.28, 2.14, 2.70 and 3.09 mg/L, there were 0/5, 2/5, 1/5, 2/5 and 2/5 deaths, respectively. The LD_{50} could not be calculated but it is > 2 mg/L (Toxicity Category IV)
NA = not available

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for Tebufenpyrad (090102)

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment	Study
Dietary Risk Assessments				
Acute Dietary females 13-50 years of age	N/A	N/A	N/A - no food uses	
Acute Dietary general population including infants and children	N/A	N/A	N/A - no food uses	
Chronic Dietary all populations	N/A	N/A	N/A - no food uses	
Incidental Oral Short-Term (1 - 30 Days) Residential Only	N/A	N/A	N/A - no residential uses	
Incidental Oral Intermediate-Term (1 - 6 Months) Residential Only	N/A N/A	N/A	N/A - no residential uses	
Non-Dietary Risk Assessments				
Dermal Short- and Intermediate - Term (1 - 30 days and 1-6 Months)	Dermal NOAEL= 200		LOAEL = 1000 mg/kg/day based on decreased bodyweight gain and food consumption in male and female New Zealand White rabbits.	21-day dermal study in the rabbit
Residential	**MOE** = N/A	N/A		
Occupational	**MOE** = 100	N/A		

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment	Study
Dermal Long-Term (> 6 Months)	Oral NOAEL[1]= 0.82		LOAEL = 6.52 mg/kg/day based on decreased body weights and body weight gain and liver toxicity in both sexes and a slight microcytic anemia and effects on the ovary in females.	Combined chronic toxicity/carcinogenicity in rats
Residential	**MOE** = N/A	N/A		
Occupational	**MOE** = 100	N/A		
Inhalation Short-Term (1 - 30 days)	Oral NOAEL[2]= 15		LOAEL = 50 mg/kg/day based on decreased body weight gain and increased water consumption.	Prenatal developmental toxicity study in rats
Residential	**MOE** = N/A	N/A		
Occupational	**MOE** = 100	N/A		
Inhalation Intermediate-Term (1 - 6 Months)	Oral NOAEL[2]= 2		LOAEL = 10 mg/kg/day based on an increased incidence of diarrhea and/or vomiting in males and females.	90-Day Capsule Study in the Dog
Residential	**MOE** = N/A	N/A		
Occupational	**MOE** = 100	N/A		
Inhalation Long-Term (>6 Months)	Oral NOAEL[2]= 1		LOAEL = 6 mg/kg/day based on vomiting and diarrhea/loose stools and thickened gastric mucosa and chronic gastritis in the pyloric region.	1-Year Capsule Study in the Dog
Residential	**MOE** = N/A	N/A		
Occupational	**MOE** = 100	N/A		
Cancer	**Classification:** Referred to CARC **Q1*** = Not yet determined			

[1] An oral NOAEL was used for an endpoint for the dermal assessment. An estimated 4% dermal absorption value will be used with the oral NOAEL.

[2] An oral NOAEL was used for an endpoint for the inhalation assessment. Inhalation absorption is assumed to be equivalent to oral absorption.

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Chemical:	**1H-Pyrazole-5-carboxamide, 4-chloro-N-((**
PC Code:	**090102**
HED File Code	**21100 HIARC**
Memo Date:	**04/25/2002**
File ID:	**TX050693**
Accession Number:	**412-02-0282**

HED Records Reference Center
06/04/2002